REMARKS

In this application, claims 89-117 are currently pending. Claims 89-110 and 114 are under examination.

Applicant appreciates Examiner Sang's time and helpful discussion in the telephonic interview conducted on October 25, 2007, with Applicant's representatives. It is believed that the response addresses the issues discussed in the interview.

Applicant respectfully traverses the rejection of claims 89-110 and 114 as allegedly rendered obvious under 35 U.S.C. § 103(a) by Froesch et al., *Proc. Am. Assoc. Cancer Res.* 89:13 (1998), in view of Takayama et al., *Cancer Res.* 58:3116-3131 (1998), Noordzij et al., *J. Urology* 158:1880-1885 (1997) and Sano et al., U.S. Patent No. 5,665,539. Applicant maintains, for the reasons of record and further as set forth below, that claims 89-110 and 114 are unobvious over Froesch et al., alone or in combination with Takayama et al., Noordzij et al. and/or Sano et al.

The Federal circuit has reaffirmed the Office's high burden to establish a *prima facie* case of obviousness and has emphasized the requirement of specificity. See *In re Sang-Su Lee,* 277 F.3d 1338, 61 USPQ 2d 1430 (Fed. Cir. 2002). In *Lee*, the Federal Circuit held that "[t]he factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record." *Id.* 277 F.3d at 1433 (emphasis added). Further, when considering differences between prior art and the claimed invention, "a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP §2141.02(VI).

Applicant respectfully maintains, for the reasons of record, that the Office has failed to provide objective evidence when maintaining that the teaching of Froesch et al. in view of Takayama et al., Noordzij et al. and Sano et al. "would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the level of BAG-1 expressed in prostate cancer using immuno-PCR, compare the level with a reference level and further correlate the results with the risk of tumor recurrence, tumor spread and survival in a patient suffering from prostate cancer" (Office Action page 5). In this passage the Office Action acknowledges that, even if one skilled in the art were to "view the teachings of Froesch,

Takayama, Noordzij and Sano" together, at best further correlation of results would be required. In such a case, clearly one skilled in the art would have had no reasonable expectation of success of achieving the claimed methods, as required to establish a *prima facie* case of obviousness.

Applicant respectfully maintains, for the reasons of record, that Froesch et al. does not teach or suggest methods for determining the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer by determining BAG-1 gene expression. At best, Froesch et al. describes the observation that BAG-1L is expressed in prostate cancers and enhances androgen receptor function. However, Froesch et al. provides no teaching or suggestion that the level of BAG-1 gene expression can be used to determine the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer by determining BAG-1 gene expression. In fact, Froesch et al. provides no teaching or suggestion of any relative expression level of BAG-1, let alone overexpression, only that BAG-1 was detected in the prostate cancer lines and archival prostate tumor specimens tested. The specification teaches that BAG-1 is expressed in normal prostate, albeit in a smaller percentage of cells (41% in normal versus 78% in cancer cells)(see specification page 41, lines 7-12). Thus, it is the subject specification, not Froesch et al., that teaches overexpression, i.e. higher intensity BAG-1 immunostaining, was found to be, for example, associated with a higher incidence of metastatic relapse (page 41, lines 4-7). Froesch et al. provides no teaching or suggestion of the level of BAG-1 expression, let alone overexpression, merely that BAG-1 is expressed in prostate cancer cell lines and tissue samples.

Applicants further maintain, for the reasons of record, that none of Takayama et al., Noordzij et al. and/or Sano et al. cure the deficiencies of Froesch et al. As discussed in the previous response filed July 23, 2007, on page 3116, right column, 2nd paragraph, lines 5-7, of the Takayama et al. reference, the quotation "BAG-1 has been shown to increase the metastatic potential of tumor cells *in vivo*" ends with footnote No. 4, which suggests that the quotation was based on an article by Yawata et al., which published as *Oncogene* 16:2681-2686 (1998) (attached as Exhibit 1 in previous response). Yawata et al. reported that overexpression of Bcl-2 or BAG-1 enhances peritoneal dissemination of human gastric MKN74 cells in nude mice (see Yawata at page 2682, left column, paragraph 1, lines 3-5; and page 2684 under the heading of *peritoneal dissemination of MKN74 transfectants*). In other words, the Takayama et al. alleged

teaching should not have been interpreted broader than its source, the Yawata et al. reference, which was available to a person of ordinary skill in the art at the time the present application was filed. For a person having ordinary skill in the art and having the capability of appreciating the complexity of scientific issues in cancer, the BAG-1 effects in dissemination of gastric cancer cells in mice could have hardly provided any reasonable expectation of success for that person to want to apply the same concept to prostate cancer in human and arrive at a method of determining the risk of tumor recurrence or spread in patients suffering from prostate cancer, as claimed. Therefore, in contrast to the Office's contention, the teaching of Takayama et al., even in combination with Noordzij et al. and/or Sano et al. would not have cured the deficiencies of Froesch et al. or rendered the claimed invention obvious.

With regard to Noordzij et al. and as discussed in the previous response, Noordzij et al. found no correlation with Bcl-2, contrary to the assertion in the previous Office Action. "The bcl-2 scores did not correlate with tumor stage or grade" (abstract). Noordzij et al. further indicated that "[A]ndrogen receptor scores were marginally related to tumor grade, but not to tumor stage" (abstract). Noordzij et al. stated that a "prognostic value of bcl-2 or androgen receptor in pretreatment transurethral resection specimens was not found" (see abstract and page 1883, right column, first complete paragraph). Noordzij et al. found only a combined bcl-2/androgen receptor score to be an independent prognostic marker to predict clinical progression (see abstract and page 1883, right column, third paragraph). Therefore, Applicant avers that Noordzij et al. cannot cure the deficiencies of Froesch et al., alone or in combination with Takayama et al. and/or Sano et al (teaching immuno-PCR).

In the Office Action on pages 4-5, the references of Yawata et al., Tang et al., *J. Clin. Oncol.* 17:1710-1719 (1999), Yang et al., *Exp. Cell Res.* 247:200-207 (1999), and Takayama et al. are described. The Office Action states on page 5:

> Therefore, in view of the teachings of prior art as Yawata, Tang, Yang, and Takayama, one of ordinary skill of art would reasonably conclude that the overexpression of BAG-1 protein promotes the cancer cell survival and is correlated with the metastatic potential of tumor cells…Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the level of BAG-1 expressed in prostate cancer using immuno-PCR, compare the level with a reference level and further correlate the result with the risk of tumor

recurrence, tumor spread and survival in a patient suffering from prostate cancer in view of the teachings of Froesch, Takayama, Noordzij and Sano.

Applicants respectfully disagree. As discussed above, Froesch et al., at best, describes that BAG-1 is expressed in prostate cancer cell lines and tissue samples but provides no teaching or suggestion that BAG-1 is overexpressed. It is Applicant's disclosure that teaches measuring the level of BAG-1 expression in prostate cancer and determining whether there is a correlation with tumor recurrence or spread. As previously submitted, a person of ordinary skill in the art who knew about the teachings of Froesch et al. and was familiar with the work of Noordzij et al. and Sano et al., after reading the Takayama et al., Yawata et al., Tang et al., and Yang et al. references, would have no reasonable expectation of success of achieving the claimed method of determining the risk of tumor recurrence or spread in a patient suffering from prostate cancer, absent the teachings in Applicant's specification.

With respect to the post-filing references submitted with the previous response and discussed in the interview, in the present Office Action it is asserted on page 4 that the references Turner et al. (*J. Clinical Oncology* 19(4):992-1000 (2001)) and Rorke et al. (*Int. J. Cancer (Pred. Oncol.)* 95:317-322 (2001)) presented as evidence in the previous response were inadmissible because they were published after the filing date of the instant application. Applicant respectfully traverses, specifically in regard to the Turner et al. reference.

According to MPEP, the objective evidence test for obviousness is not restricted to the art that was available at the time of filing the patent application. See MPEP § 2141(III) citing *Knoll Pharms. Co., Inc. v. Teva Pharms. USA Inc.,* 367 F.3d 1381, 1385, 70 USPQ2d 1957, 1960 (Fed. Cir. 2004) (holding that the information published post filing can be proof of what existed physically at time the application was filed).

Turner et al., published by Applicant in February 2001, was a report based on what was disclosed in U.S. application serial No. 09/350,518, filed July 09, 1999, and the present application. The filing date of the present application is July 7, 2000 (international filing date of PCT/US00/18758, which claims priority to U.S. application serial No. 09/350,518). Although Turner et al. was published in 2001, Applicant maintains that it is relevant to the state of knowledge that existed at the time of filing of the application. Accordingly, to be objective in its

assessment of obviousness, the Office must consider the teachings of Turner et al. Furthermore, in view of the knowledge that BAG-1 expression had opposite effects in different cancers, a person of ordinary skill in the art at the time the invention was made, could not have been certain about any correlations of BAG-1 expression with host survival, let alone have a reasonable expectation of success of achieving the claimed methods.

In conclusion, Applicant submits that in view of the above-stated remarks and for the reasons of record, a *prima facie* case of obviousness has not been established with respect to the invention as claimed. A person of ordinary skill in the art would not have been motivated nor would have had a reasonable expectation of success to combine the teachings of Froesch et al. with those of Takayama et al., Noordzij et al. and/or Sano et al. to arrive at the claimed methods. Therefore, Applicants respectfully maintain that the claimed methods are unobvious over Froesch et al., alone or in combination with Takayama et al., Noordzij et al. and/or Sano et al. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 89-110 and 114 as allegedly rendered obvious under 35 U.S.C. § 103(a).

In light of the remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP

/Deborah L. Cadena/

Deborah L. Cadena
Registration No. 44,048

4370 La Jolla Village Drive, Suite 700
San Diego, CA 92122
Phone: 858.535.9001 DLC:llf
Facsimile: 858.597.1585
Date: March 5, 2008

Please recognize our Customer No. 41552 as our correspondence address.